Remarks

Claims 1, 11, 20, 21, 24, 31, 102 and 103 have been amended. Support for these amendments can be found in the specification on page 3 lines 11-14, page 5 lines 26-31, page 14 line 4, page 16 lines 9-15, page 16 lines 16-22, page 18 lines 25-26, page 20 lines 19-20 and page 35 lines 28-30 (claims 1 and 31); and page 36 lines 2-7 (claim 11). Claims 20, 21, 102 and 103 are amended to recite proper antecedent basis. Claim 24 is amended to correct a typographical error.

Claims 7-9, 12-15, 100 and 101 are cancelled.

New claims 104-111 are added. Support for these claims can be found on page 18 lines 25-27 (claims 104 and 105); page 18 lines 29-31 (claim 106); page 6 lines 3-8, page 13 lines 23-24 and in the Examples (claims 107 and 108); page 36 lines 23-33 through to page 38 (claims 109 and 110); and page 40 lines 25-33 and page 41 lines 1-7 (claim 111).

No new matter has been added.

Claims 1-6, 10, 11, 16-31, 52 and 102-111 are pending. No additional claims fees are considered due.

Rejection under 35 U.S.C. §112

Written Description

Claims 1-31, 52 and 100 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner apparently bases his rejection on the fact that the claims "are neither limited to a particular sequence or common structure of a … Th2 immunostimulatory nucleic acid, nor to a particular route of administration, nor to IgG2a antibodies or IgA production". The Examiner characterizes the claimed nucleic acids as having no chemical structure.

Applicant respectfully disagrees and wishes to correct some of the Examiner's statements. First, claim 1 and claims dependent thereon require either mucosal or dermal administration and thus are limited to particular routes of administration. Claim 31 requires

parenteral administration and thus is also limited to a particular route of administration. Accordingly, the instant claims are restricted to particular routes of administration.

Second, the claimed method induces Th2-biased immune responses which, as described in the specification at least on pages 3, 14, 16 and 17, are characterized by a particular biased cytokine and antibody profile that includes IgG1 and IgE. More particularly, the Th2-biased immune response is characterized as a greater induction of Th2 than Th1 antibodies (e.g., IgG1 >> IgG2). (See at least page 14.) Accordingly, the instant claims, which relate to Th2-biased immune responses, would not recite IgG2a antibodies, as suggested by the Examiner, since such antibodies are associated with Th1 immune responses. In addition, IgA antibodies are associated with a mucosal immune response and may or may not be generated in the context of a Th1 and/or a Th2 immune response. Thus, it is not necessary that claims 1 and 31 recite IgA since a Th2-biased immune response can be induced irrespective of IgA production.

The Examiner further asserts that the nucleic acids of the invention have no chemical structure. The instant claims relate to the use of nucleic acids which when administered by a particular route (and in some instances, at a particular dose) stimulate a Th2-biased immune response. The nucleic acids are of a particular length and they lack the Th1 immunostimulatory motifs of CpG dinucleotides, poly T motifs and poly G motifs. The structure of a nucleic acid is known in the art. The structures of the Th1 immunostimulatory motifs are known. The induction of a Th2-biased immune response is independent of the sequence of the nucleic acid, apart from the Th1 immunostimulatory motifs.

The Examiner cites Zhao et al. (Antisense & Nucleic Acid Drug Development, 7:495, 1997) for the proposition that "the prior art consistently teaches and discloses that the immune stimulatory effect was dependent on the sequence and physiochemical properties of the oligonucleotides". Respectfully, Zhao et al. is a paper directed to the analysis of Th1 immune responses. It reported that one CpG containing oligonucleotide (oligo 1) upregulates Th1, but not Th2, cytokines. It further compared the ability of another CpG containing oligonucleotide (oligo 2) and an oligonucleotide lacking a CpG dinucleotide (oligo 3) to induce IL-12, and reported that oligo 2 increased serum IL-12 levels, while oligo 3 did not. It concluded that IL-12 induction was sequence dependent. These findings are not inconsistent with the claimed invention. The reference reported that an oligonucleotide lacking a CG dinucleotide failed to

induce a Th1 cytokine. It said nothing of the ability of such oligonucleotide to stimulate a Th2 immune response.

The Examiner relies on Fiers v. Revel 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993) and Regents of University California. v. Eli Lilly & Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) for the proposition that "an adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, ... not a mere wish or plan for obtaining the claimed chemical invention". Respectfully, the claims at issue in Fiers and Eli Lilly relate to nucleic acids that encode proteins, and thus such nucleic acids are necessarily defined by their sequence. In effect, the Courts were saying that not every nucleic acid would code for the desired protein. This must be contrasted with the nucleic acids of the instant claims which do not encode a protein. The instant claims recite an oligonucleotide that induces a Th2-biased immune response independent of sequence apart from the exclusion of Th1 immunostimulatory motifs as recited in the claims. Thus, apart from such exclusion, there is no sequence requirement or limitation as any nucleic acid when administered mucosally or dermally (or parenterally at higher doses) will generate a Th2-biased immune response. The invention is based in part on this remarkable finding.

The structure of nucleic acids is known. There is no particular sequence limitation required of the claimed nucleic acids, apart from the exclusion of the afore-mentioned Th1 motifs. Such Th1 motifs are taught in the specification. The mode of administration is described. Accordingly, the specification satisfies the written description requirement.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, written description, is respectfully requested.

Enablement

Claims 1-31, 52 and 100 are rejected under §112, first paragraph, because according to the Examiner the specification "while being enabling for (a) method of mucosally administering Th2 immunostimulatory nucleic acid comprising SEQ ID NO:1 in combination with an administration of an antigen to subject ... does not reasonably provide enablement for any other claimed embodiment".

Applicant respectfully disagrees.

The test of enablement is whether undue or unreasonable experimentation is required for one of ordinary skill in the art to practice (i.e., make and use) the claimed invention. Thus, based on the specification and the knowledge in the art at the time of filing (i.e., effective filing date), one of ordinary skill must be able to make and use the claimed invention without undue experimentation. The experimentation may be complex and still not be undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive of the issue of enablement. Applicant previously provided a Wands analysis in the context of the claimed invention, and the Examiner is referred thereto.

The enablement rejection fails at least for two reasons. First, the Examiner has failed to meet his burden regarding a prima facie case of enablement. Second, contrary to the Examiner's assertions, the references cited by the Examiner as evidence of the state of the art are not inconsistent with the claimed invention and/or are not reflective of the state of the art at the time of filing. Applicant addresses each of these issues in greater detail below.

Although the Wands factors must be considered in their totality with no one factor being dispositive, the Examiner has maintained the enablement rejection apparently based solely on the state of the art at the time of filing. The Examiner apparently has not considered the factors in their totality, and thus has failed to meet his burden of establishing a prima facie case of lack of enablement. The rejection is therefore improper solely on this basis and should be withdrawn.

Notwithstanding this, and in the interest of expediting prosecution, Applicant addresses the rejection. According to the Examiner, the state of the art prior to the filing date of the application relates mainly to expression vectors that contain CG dinucleotides, palindromic oligos for the treatment of tumors, and unmethylated CpG containing oligos as Th1 adjuvants. In view of this art, the Examiner questions "whether or not a skilled artisan … would have reasonably be able to extrapolate the rather unexpected results as demonstrated by the as-filed

specification to the full breadth of the claim". The Examiner has cited several references as evidence of the state of the art at the time of filing. As discussed in greater detail below, these references are not inconsistent with the claimed invention and/or do not reflect the state of the art at the time of filing. Applicant addresses each reference in the context of the claimed invention.

Yamamoto et al. (Antisense Research and Development, 4:119, 1994) is cited for the teaching that "the use of a specific palindromic sequence and some molecular size of synthetic oligoDNA is required to induce … biological activity". Yamamoto et al. reported the ability of CpG containing oligonucleotides to induce markers of a Th1 immune response (e.g., production of IFN and augmentation of NK cell activity). Neither the oligonucleotides nor the readouts of Yamamoto et al. relate to the claimed invention.

Messina et al. (Cellular Immunology, 147:148, 1993) is cited for the teaching that "at present, the mechanism by which DNA triggers proliferation is not known (and that) since only certain natural as well as synthetic DNA are active, it appears that mitogenicity results from an interaction with high ligand specificity rather than simple binding of DNA to cells on the basis of charges". First, understanding or identifying the mechanism for a claimed invention is not a prerequisite to patentability. Second, the *in vitro* experiments of Messina et al. failed to show immunostimulatory effect of certain nucleic acids. Applicant has already stated in the instant application that the Th2 immune stimulation observed *in vivo* was surprising at least because the same nucleic acids were inert *in vitro*. (See, for example, page 14, lines 1-6.) Accordingly, the teachings of Messina et al. are nonetheless not inconsistent with the claimed invention.

Branda et al. (J. Laboratory and Clinical Medicine, 128(3):329, 1996) is cited for the teaching of lack of homology between B cell stimulatory oligonucleotides and lack of immunoinhibitory or neutralizing effects. Branda et al. reports the results of both *in vitro* and *in vivo* experiments using CG and non-CG containing oligonucleotides. As argued above, the lack of an observed immune effect *in vitro* by non-CG containing oligonucleotides (e.g., see compounds 6 or 7) is not inconsistent with the claimed invention. The lack of an observed immune effect *in vivo* by non-CG containing oligonucleotides (e.g., see compounds 35 or 36) administered intravenously is also not inconsistent with the claimed invention. As stated in the specification, greater amounts of Th2 immunostimulatory nucleic acids had to be administered parenterally to observe the immunostimulatory effects observed after mucosal administration.

(See, for example, page 13, lines 30-32.) The amounts used by Branda et al. therefore may not have been optimal. Neither the *in vitro* nor the *in vivo* data reported by Branda et al. is inconsistent with the claimed invention.

McCluskie et al. (Vaccine, 19:413, 2001) has been cited for the teaching that immunostimulation by non-CG containing oligonucleotides was "totally unexpected since non-CpG ODN do not have such an effect when delivered by a parenteral route". Applicant wishes to point out that McCluskie et al. shares much of the data from the instant application, and accordingly its teachings are, if anything, consistent with those of the instant application. As stated above, parenteral administration of Th2 immunostimulatory oligonucleotides at low doses (such as those effective to stimulate a Th1 immune response by CpG oligonucleotides) does not result in Th2 immune stimulation, and higher doses are necessary.

McCluskie et al. (Vaccine, 19:2657, 2001) has been cited for the teaching that the immunostimulatory properties of non-CpG oligonucleotides do "not appear to be due solely to the phosphorothioate backbone … but rather a sequence-related effect, since phosphorothioate poly-T and poly-GC ODN of similar size do not have such an immunostimulatory effect". Applicant notes that the recitation of "poly-GC" in the reference is apparently a typographical error and should be "poly-CG", as supported by the data. In fact, the data show that the two non-CG containing oligonucleotides (which also lack a poly-T motif and a poly-G motif) are Th2 immunostimulatory. The statement from McCluskie et al. relates to nucleic acids excluded from the instant claims and therefore is moot. The results of the reference are consistent with the claimed invention.

McCluskie et al. (J. Immunology, 161:4463, 1998) has been cited for the teaching that non-CG oligonucleotides stimulated no or very low levels of anti-HBs IgG antibodies and no significant levels of fecal IgA. The teachings of McCluskie et al. are not inconsistent with the claimed invention. The oligonucleotide and antigen doses reported by McCluskie et al. were lower than those used in the instant specification. One of ordinary skill in the art would expect to optimize nucleic acid and antigen doses prior to use, as a matter of routine. Such optimization is not inconsistent with the claimed invention.

Zhao et al. (Antisense & Nucleic Acid Drug Development, 7:495-502, 1997) is cited for the teaching that whether or not "induction of an immune response such as IL-12 can be

generated by a CpG based oligo and non-CpG based oligo remains reasonably unpredictable at best", and that "a non-CpG based oligo (referred to as oligo 3) does not induce a cytokine production, e.g., IL-12". As stated above, IL-12 production is associated with a Th1 immune response. The claimed invention relates to a Th2 immune response and accordingly IL-12 production would not be expected. Prior art teachings that non-CG oligonucleotides do not stimulate a Th1 immune response are not inconsistent with the claimed invention.

McCluskie et al. (Molecular Medicine, 5:287-300, 1999) is cited for various teachings relating to DNA vaccines, including that noninjected (e.g., mucosal) routes of DNA vaccine delivery did not yield immune responses. These teachings are not relevant, but neither are they inconsistent, with the claimed invention which does not relate to DNA vaccines. DNA vaccines function by encoding an antigen that is expressed within cells. To be effective, DNA vaccines must (a) remain intact, (b) enter the nucleus of target cells, and (c) produce their encoded protein, which in turn must be presented to the immune system. None of these functions are required of the claimed Th2-immunostimulatory nucleic acids. The instant claims recite nucleic acids 6-100 nucleotides in length that may be single or double stranded. The claimed nucleic acids nucleic acids therefore are not plasmids, nor are they DNA vaccines, which are typically > 5000 nucleotides in length and are double-stranded.

The Examiner highlights statements in the instant specification relating to the lack of immune stimulation following parenteral administration of non-CpG oligonucleotides. A full reading of the specification would have clarified the point for the Examiner. The specification repeatedly states that the invention is premised in part on the finding that Th2 immunostimulatory nucleic acids generate a Th2 immune response when administered parenterally *in higher amounts*. (See, for example, page 4 lines 11-16.) The Examiner however asserts that one of ordinary skill based on the prior art of record "would not have reasonably believed that such could be done". The prior art of record is generally not inconsistent with the claimed invention and it therefore does not support the Examiner's position regarding enablement.

Applicant also notes that the Examiner repeatedly refers to the "unexpected results" provided by the specification as a basis for lack of enablement. That results are unexpected is not a basis for lack of enablement, particularly where data evidencing such results are provided.

The Examiner cannot simply doubt such data and rather must provide a basis for questioning its veracity.

In summary, the claimed invention relates to induction of Th2-biased antigen-specific immune responses by administering mucosally, dermally or parenterally a Th2 immunostimulatory nucleic acid and an antigen in a carrier to a subject in need of such an immune response. One of ordinary skill in the art will be able to make and administer such nucleic acids at least based on the guidance provided by the specification. The use of Th1 immunostimulatory oligonucleotides for inducing Th1 immune responses was known at the time of filing, as evidenced by the art of record. Accordingly, the art was familiar with the ability of oligonucleotides to generate immune responses. The structure of nucleic acids of a defined length and lacking particular sequence motifs would also be known to one of ordinary skill in the art, as would be a method for their synthesis. Accordingly, the specification enables the full scope of the claimed invention.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, enablement, is respectfully requested.

Summary

In view of the foregoing, the claims are considered to be in condition for allowance. A notice to that effect is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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